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**Attractive Non-Covalent Interactions in Asymmetric Catalysis: Links Between Enzymes and Small-Molecule Catalysts**

Robert R. Knowles and Eric N. Jacobsen\*

*Department of Chemistry & Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138*

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## Abstract

Catalysis by neutral, organic, small molecules capable of binding and activating substrates solely via non-covalent interactions—particularly H-bonding—has emerged as an important approach in organocatalysis. The mechanisms by which such small-molecule catalysts induce high enantioselectivity may be quite different from those employed by catalysts that rely on covalent interactions with substrates. Attractive non-covalent interactions are weaker, less distance-dependent, less directional, and more affected by entropy than covalent interactions. However, the conformational constraint required for high stereinduction may be achieved, in principle, if multiple non-covalent attractive interactions are operating in concert. This perspective will outline some recent efforts to elucidate the cooperative mechanisms responsible for stereinduction in highly enantioselective reactions promoted by non-covalent catalysts.

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## Introduction

Attractive non-covalent interactions play a central role in pharmaceutical design, supramolecular chemistry, molecular biology, sensing applications, materials, crystal engineering, and a host of other fields in the chemical sciences.<sup>1-8</sup> As a result of this broad importance, intensive research efforts have been directed towards elucidating and quantifying these interactions, which include hydrogen bonding, electrostatic effects, pi-pi, cation-pi, hydrophobic, and Van der Waals forces.<sup>9-14</sup> These studies have focused primarily on molecular recognition phenomena, shedding light on the thermodynamic stabilization of bound complexes. Attractive non-covalent interactions also play a key role in catalysis by lowering the kinetic barriers to reactions through transition-state stabilization.<sup>15, 16</sup> In fact, these forces are responsible for many of the remarkable rate accelerations and stereoselectivities characteristic of enzymatic catalysis, wherein cooperative non-covalent interactions with specific active site residues can stabilize the electrostatic character of a bound transition structure complex (e.g. Figure 1).<sup>17</sup>

While enzymes are understood to achieve selectivity through transition state stabilization, with the rate of the dominant pathway preferentially accelerated relative to competing reactions, small-molecule chiral catalysts are generally proposed to follow a

fundamentally different principle for achieving enantioselectivity. The vast majority of stereochemical models for small-molecule catalysts invoke steric interactions as a rationalization for energetic differentiation of the pathways leading to enantiomeric products (e.g. Figure 2).<sup>18-21</sup> In this conceptual framework, it is generally understood that transition state assemblies leading to the undesired configuration of the product are destabilized by repulsive steric interactions with substituents on the catalyst. Consequently, only the transition states that avoid these steric interactions are kinetically viable. The question of whether selectivity is achieved primarily through stabilizing or destabilizing interactions represents a fundamental difference in the way macromolecular and small-molecule catalysts are thought to operate.

Steric interactions – as modeled by the Lennard-Jones potential – are strongly distance dependent, such that the destabilizing effect can be alleviated by a very small reorganization (Table 1).<sup>22</sup> As such, steric destabilization is most effective as a defining element of stereocontrol in strongly bound and conformationally restricted complexes, where any structural reordering away from equilibrium incurs a substantial energetic penalty. This is generally the case in reactions mediated by organometallic complexes, Lewis acids, secondary amines and other important classes of small-molecule catalysts, where transition structures are associated to the catalyst through well-defined covalent interactions (Figure 2).

By contrast, non-covalent interactions are not only generally weaker, but also less directional and less distance-dependent than covalent and dative bonds (Table 1).<sup>23</sup> As such, in a complex where a catalyst interacts with its substrate through a single non-covalent interaction, many geometrical orientations of the substrate relative to the catalyst may be very similar in energy. Thus, significant structural reorganizations can occur without energetically destabilizing the binding interaction to any large extent. Such a lack of conformational order presents an obvious challenge to achieving high enantioselectivity. This may be overcome, in principle, through implementation of multiple non-covalent attractive interactions operating in concert, as this can afford the conformational constraint required for high stereinduction.<sup>24,25</sup> This cooperative model of binding is a defining feature of both biological and synthetic receptors, and also underlies enzymatic catalysis.

Several well-known asymmetric catalytic processes involving Lewis acids and transition metals have invoked attractive non-covalent interactions as elements of stereocontrol, including the Sharpless dihydroxylation, the Noyori transfer hydrogenation, and Corey's oxazaborolidine-catalyzed cycloadditions.<sup>26-28</sup> However, over the past decade, remarkably simple organocatalytic systems have been identified that operate exclusively through non-covalent interactions and yet induce high levels of enantioselectivity in synthetically important transformations. Elucidation of the attractive forces acting in concert in such systems presents a significant challenge to modern mechanistic chemistry, but one that appears well-justified given the design principles and general insights into non-covalent interactions that could emerge. Here we discuss four chiral hydrogen-bond donor catalyst systems developed in our laboratories that have begun to provide a wealth of information in that regard.

## Discussion

### Claisen Rearrangement

Rate enhancement of the Claisen rearrangement by hydrogen-bond donors is known to occur in enzymatic systems (Figure 1) and has also been demonstrated with protic solvents and electron-deficient diaryl ureas (Figure 3).<sup>29-31</sup> The observed accelerations are most pronounced with allyl vinyl ethers bearing electron-withdrawing and/or electron-donating substituents, an effect attributable to the notion that such substrates undergo rearrangement through polar transition states with substantial 'enolate'/'allyl cation' character. Electrostatic stabilization of the transition state can be imparted through H-bond interactions, which disperse the augmented anionic character of the partially broken C–O bond.<sup>32-34</sup>

With this precedent in mind, we sought to develop a chiral H-bond donor catalyst system for enantioselective Claisen rearrangements.<sup>35</sup> Substoichiometric quantities of diols, phosphoric acids, or thioureas were not found to induce measurable rate accelerations, but cationic diphenyl guanidinium ion displayed significant catalytic activity in rearrangements of a diverse range of electronically activated allyl vinyl ethers. Extensive development and optimization studies led to the identification of chiral C<sub>2</sub>-symmetric guanidinium ion (**3**) as an effective and general catalyst for highly

enantioselective Claisen rearrangements of ester-substituted allyl vinyl ethers (Figure 4).<sup>35</sup>

Structural and computational investigation into the origins of enantioselectivity indicates that several attractive non-covalent interactions may be acting in concert to serve as the basis for stereoinduction in these transformations. In the lowest-energy conformation of the catalyst, both pyrrole rings of **3** are engaged in cation- $\pi$  interactions with the cationic  $\text{NH}_2$  of the guanidinium ion, splaying the pendant phenyl substituents of the pyrrole into an orientation that creates a well-defined box-like space surrounding the H-bond donor functionality (Figure 4). In this conformation, the catalyst is found to bind to substrate **1** through a dual hydrogen bonding interaction to both the ether and ester oxygens. This two-point binding interaction serves to order the geometry of the complexation, and the presence of the ester substituent also increases the degree of charge separation in the rearrangement transition state.

As noted above, this increased polarization introduces cationic character on the allyl fragment of the transition state as well. Computational modeling indicates that this cationic character is engaged and stabilized by the catalyst phenyl rings through a cation- $\pi$  interaction in only one of the two competing diastereomeric transition states (Figure 4). This intriguing rationale for stereoinduction was tested experimentally through the preparation and evaluation of aryl-substituted derivatives of **3**. Dimethylamino-substituted catalyst **5** induced increased enantioselectivity relative to the parent catalyst, while the corresponding fluorophenyl derivative **4** proved less enantioselective (Table 2). This lends direct support to the hypothesis that differential transition state stabilization responsible for enantioselectivity is achieved through intermolecular cation- $\pi$  interactions.<sup>36,37</sup>

This chiral guanidium-catalyzed Claisen rearrangement reaction highlights the potential of spatially-resolved transition state charge recognition to serve not only as a basis for rate acceleration, but also, to the extent that the recognition stabilizes one diastereomeric transition state preferentially, as a design principle for stereoinduction in non-covalent catalysis.

## Cationic Polycyclizations

Enantioselectivity in the catalytic Claisen rearrangement described in the previous section relies on selective catalyst stabilization of transition states bearing a relatively small degree of charge separation. In principle, cooperative non-covalent interactions may be accentuated in reactions involving fully ionic intermediates and transition states, and in the past few years a variety of urea- and thiourea-catalyzed enantioselective transformations of cationic electrophiles has been reported.<sup>38-41</sup> The success of these processes is predicated on the ability of the urea or thiourea catalyst to bind the anion associated with the positively charged electrophile through hydrogen-bond interactions (Figure 5). In non-polar media where ion pairing is particularly strong, this binding ensures that the chiral catalyst remains in close proximity to the cationic electrophile during the enantioselectivity-determining step of the catalytic cycle.

In order for the catalyst to achieve the high degree of transition state organization necessary for high enantioinduction, the presence of secondary binding elements capable of directly engaging and stabilizing the cationic character of electrophilic species has proven critical. This is illustrated in a particularly striking way in the aryl-terminated bicyclization of hydroxylactam derivatives such as **6**, catalyzed by thiourea derivatives **8-11** (Figure 6).<sup>37</sup>

The design of this system was inspired by recent advances in the understanding of biosynthetic polyene cyclizations. In these enzymatic transformations, olefins in a polyunsaturated substrate undergo sequential additions to pendant carbocations to generate structurally and stereochemically complex polycyclic products. Mechanistic and structural studies of relevant enzymes such as oxidosqualene cyclase have provided strong evidence that the cationic intermediates and transition states in these cyclizations are stabilized by cation- $\pi$  interactions with aromatic residues within the enzyme active site.<sup>43-46</sup>

In line with this biosynthetic proposal, we explored the construction and application of thiourea catalysts bearing specifically positioned aryl substituents that could engage in analogous cation- $\pi$  interactions to direct the stereochemical course of a cationic polycyclization. In the model bicyclization reaction of hydroxylactam derivative **6** (Figure 6), it was discovered that both the reactivity and degree of asymmetric

induction observed in these transformations was strongly correlated with the expanse of the arene within a common catalyst framework, with larger arenes proving more effective. Given the cationic nature of the reaction and fact that larger polycyclic aromatic hydrocarbons bind cations more strongly than their smaller analogues, this trend suggested that stabilizing cation- $\pi$  interactions were profoundly influencing the degree of asymmetric induction.<sup>47</sup>

Several experimental results and observations offer support for this hypothesis. The ‘strength’ of an attractive non-covalent interaction is generally reflected in the enthalpic contribution to the free energy of association.<sup>48</sup> As such, if the larger arenes were indeed engaging in stronger or more extensive cation- $\pi$  interactions in the dominant transition state structure, this should be manifested in the differences in the magnitude of the differential enthalpy term between the more and less enantioselective catalysts. Consistent with this reasoning, an Eyring analysis of enantioselectivity for catalysts **9**, **10**, and **11** revealed that the degree of asymmetric induction in these reactions was enthalpically controlled and that the extent of the differential enthalpy increased dramatically with the increasing size of catalyst arene (Figure 7). A corresponding and opposing increase in the differential enthalpy terms across the series was also observed, consistent with the greater degree of differential transition state ordering expected as a consequence of a stronger non-covalent interaction. Moreover, it was found that the degree of enantioselectivity observed under a standard set of conditions for catalyst **8–11** correlated with the quadrupole moment and polarizability of the arene found in each of these catalysts (Figure 7). As these two molecular properties dictate the strength of the electrostatic and dispersion components of the cation- $\pi$  interaction, these correlations offer further support for the view that stabilizing cation- $\pi$  interactions are a principal determinant of enantioselectivity in these transformations.<sup>37,49,50</sup>

The examples provided above underline the potential importance of cation- $\pi$  interactions in differential stabilization of competing diastereomeric transition states. Given these observations, it would be reasonable to expect that other types of stabilizing electrostatic interactions could play a role in controlling the stereochemical outcome of organocatalytic reactions of cationic intermediates. Indeed, as illustrated in the following two examples, cation stabilization by weakly basic substituents in thiourea and urea



catalysts has been found to play a pivotal role in the mechanisms of synthetically valuable enantioselective reactions.

## Strecker Reaction

In the course of exploring simple chiral thiourea derivatives as potential catalysts for the hydrocyanation of imines, we observed a remarkable effect of the structure of the tertiary amide group on enantioselectivity (Figure 8).<sup>51</sup> Thiourea **16** proved to be a practical and broadly applicable catalyst for the Strecker reaction using either TMSCN or KCN as the cyanide source.<sup>52</sup> An extensive kinetic and computational analysis of the mechanism of this transformation revealed that differential cation stabilization afforded by the amide carbonyl of catalyst **16** plays a prominent role in directing the stereochemical course of these transformations (Figure 8).

Hammett studies, catalyst structure/activity relationships, and computational investigations paint a consistent mechanistic picture wherein the addition of HCN to imines mediated by **16** proceeds through a catalyst-bound cyanide/iminium ion pair (Figure 9). In this pathway, which is qualitatively similar to the proposed mechanism for Strecker reactions carried out in protic solvents, a thiourea-bound HCN (or HNC) first transfers its acidic proton to the imine substrate.<sup>53</sup> The resulting contact ion pair then undergoes rearrangement to separate the charged species, which is accomplished by transferring the hydrogen bonding interaction of the protioiminium ion N-H from the bound cyanide to the carbonyl of the catalyst amide. This charge-separated pair then collapses to form the  $\alpha$ -aminonitrile product (Figure 9).

Charge separation is energetically costly in non-polar media, and the ability of the polar functionality of the catalyst to facilitate this event is a plausible rationale for catalysis. Yet in addition to being rate-limiting, this rearrangement is also enantioselectivity-determining in that the resulting isomeric ion pairs collapse to product stereospecifically. Transition state structures for the rearrangement step leading to each enantiomer of the product were identified computationally for eight structurally distinct amido(thio)urea catalysts. In every case, the calculated enantioselectivities were found to correlate well with the values obtained experimentally, providing strong support for the

validity of the computational analysis and the accuracy of the proposed mechanism (Figure 10).

In an effort to elucidate the basis for asymmetric induction, we undertook an analysis of the structural and geometric features of the non-covalent interactions associating these competing rearrangement transition states with the catalysts. The degree of stabilization of the cyanide nucleophile was found not to correlate with the observed levels of enantioselectivity, as the sum of the bond lengths between the bound cyanide and the two (thio)urea protons are essentially equal in the transition states leading to both the (*R*) and (*S*) enantiomers for all the catalysts examined ( $d1 + d2$ , Figure 10). However, the relative stabilization of the iminium cation in the rearrangement transition states was found to correlate strongly with the calculated and observed enantioselectivities. Specifically, in the most enantioselective catalysts, the lengths of the stabilizing hydrogen bonds to the N-H of the protoiminium ion from the amide carbonyl and the cyanide anion, ( $d3 + d4$ , Figure 10) are shorter, and consequently more stabilizing, in the lower energy transition state assembly than are the analogous hydrogen bonds in the minor pathway. The steric demand of the catalyst amino acid and amide substituents prevent the minor assembly from accessing an optimal hydrogen bonding arrangement. This represents a well-characterized example of the manner in which stabilizing and destabilizing non-covalent interactions can act in concert to energetically differentiate qualitatively similar catalyst-ion pair complexes as means of achieving high enantioselectivity.

### Povarov Reaction

While the Strecker reaction proceeds through a transient, catalyst-bound iminium/cyanide pair that rapidly collapses to form product, it stands to reason that iminium ions coupled with less nucleophilic anions may persist as catalyst-bound intermediates if the energetics of the complexation are sufficiently favorable. This manner of strong ground state stabilization was found to be a key mechanistic aspect of enantioselective Povarov reactions between *N*-arylimines and electron-rich olefins co-catalyzed by sulfonic acids and sulfinamide urea **21** (Figure 11).<sup>54</sup> These reactions

proceed through highly reactive iminium sulfonate intermediates, which participate readily in [4+2] cycloadditions with electron-rich dienophiles, such as dihydrofuran, in the absence of any additional catalyst (Figure 11). However, these ion pairs also form strong non-covalent complexes with sulfinamide urea **21**, wherein the sulfonate anion is hydrogen bonded in a bidentate fashion to the urea, and the iminium formyl and N-H protons are simultaneously engaged in H-bonding interactions with the sulfonate and sulfinamide oxygens (Figure 11).<sup>55</sup>

These complexed iminium ions also undergo cycloaddition, but at rates several times slower than those observed for the corresponding unbound ion pairs. This kinetic disparity arises because catalyst **21** stabilizes the iminium sulfonate complex more strongly than it stabilizes the cycloaddition transition state, leading to rate *deceleration* in the catalytic pathway relative to the background reaction (Figure 12). Attenuation of the reactivity of a highly reactive intermediate by a catalyst finds precedent in enzymology, and has been termed “negative catalysis.”<sup>56</sup> Normally, such a situation would preclude achieving high enantioselectivity as the starting material would be consumed in the racemic pathway preferentially. However, the total iminium ion concentration never exceeds that of the catalyst **21** because of the use of catalytic levels of Brønsted acid, and the equilibrium of association for the iminium sulfonate and catalyst **21** so strongly favors the ternary complex **22** that the concentration of free iminium sulfonate in solution is vanishingly small. Thus, despite proceeding at a rate substantially slower than the competing racemic pathway, the conversion of the substrate to product is channeled entirely through the asymmetric reaction pathway involving the catalyst bound ion-pair.

Further kinetic and computational investigations were undertaken to elucidate the basis for stereoselectivity in these reactions. These studies indicate that the N-H...O<sub>sulfinamide</sub> and C-H...O<sub>sulfonate</sub> hydrogen bonding interactions observed in the ground state complex are maintained in the transition state structures and that the cycloaddition step is an asynchronous but concerted process. Enantioselectivity arises through the agency of a stabilizing pi-pi interaction between the (bis)trifluoromethylphenyl group of the catalyst and aniline arene of the substrate that is observed in the transition state

leading to the major enantiomer of the product, but which is not present in the competing diastereomeric transition state (Figure 13).

This reaction provides another demonstration of how multiple, weak non-covalent interactions can operate cooperatively in a small molecule catalyst to stabilize a highly reactive intermediate in a synthetically useful context. More broadly, the use of a strong protic acid in conjunction with a second ion-binding catalyst offers a novel and potentially general approach to inducing asymmetry in reactions that proceed through similar specific-acid mechanisms.

## Conclusions

The four systems described in this perspective illustrate some of the different ways that small molecule catalysts can promote enantioselective reactions solely through the agency of non-covalent interactions. The relatively small size of the organic catalysts and the availability of improved methods for modeling electrostatic forces render these reactions well-suited to theoretical characterization. Direct correlation of computed and experimentally-determined structure/selectivity relationships offers strong validation for the accuracy of a given mechanistic hypothesis. Full elucidation of the basis for stereoinduction remains extremely challenging, but is a necessary step in the ultimate quest for rational catalyst design. As such, the combination of experimental and computational methods to elucidate catalytic mechanisms and elements of stereocontrol will likely continue to increase in importance as an enabling aspect of research in organocatalysis.

On a fundamental level, these systems demonstrate how high enantioselectivity is tied directly to the capacity of the catalysts to induce differential stabilization of charge distributions in competing diastereomeric transition structures. This capacity arises from the engagement of cooperative mechanisms by the multifunctional catalysts, wherein multiple, spatially resolved, non-covalent interactions operate collectively to stabilize the charge-separated character of one diastereomeric transition state selectively. While this manner of electrostatic complementarity has long been recognized as a central feature of the macromolecular structures of enzymes, the examples provided here show how relatively simple, low molecular weight organic catalysts can readily accommodate all

the functionality necessary to do so as well. There is likely great future opportunity in applying transition state stabilization strategies in organocatalyst design.

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## Figure Titles

**Figure 1:** Non-covalent interactions between a transition state analog and active site residues of chorismate mutase. These attractive interactions stabilize the electrostatic character of the pericyclic transition state converting chorismate to prephenate, resulting in rate accelerations of up to  $10^6$ .

**Figure 2:** Stereochemical models for synthetically important enantioselective transformations wherein stereoselectivity is rationalized through steric destabilization of minor pathways.

**Figure 3:** Examples of rate acceleration in Claisen rearrangements of polarized allyl vinyl ethers facilitated by hydrogen bonding interactions.

**Figure 4:** Diastereomeric transition structures for the enantioselective Claisen rearrangements of ester-substituted allyl vinyl ether **1** catalyzed by guanidinium **3** calculated using density functional theory (B3LYP 6-31G). Hydrogen bonding interactions are indicated in black and the stereodifferentiating cation- $\pi$  interaction is highlighted in red.

**Figure 5:** Generalized reaction scheme for anion-binding thiourea catalysis.

**Figure 6:** Effects of catalyst aromatic group on the efficiency and enantioselectivity of the polycyclization of hydroxylactam **6**.

**Figure 7:** **a)** Differential activation parameters for the competing diastereomeric pathways in the polycyclization of hydroxylactam **6** catalyzed by **9**, **10**, and **11**. These values were derived from an Eyring analysis of enantioselectivity over a temperature range of 70 °C. **b)** and **c)** linear correlations between  $\ln(er)$  and the polarizability and quadrupole moment of the catalyst aromatic group obtained for the reaction of **6** with catalysts **8–11** under the reaction conditions described in Figure 6.

**Figure 8:** Effect of tertiary amide structure on enantioselectivity in the thiourea-catalyzed hydrocyanation of imine **12**.

**Figure 9:** Proposed mechanism for the thiourea-catalyzed Strecker reaction.

**Figure 10:** Correlation of transition structure bond lengths with enantioselectivity for Strecker reactions of imine **12**. Plots of the sum of the cyanide-(thio)urea H-bond lengths ( $d_1 + d_2$ , left) and cyanide *N*-iminium H + amide *O*-iminium H bond lengths ( $d_3 + d_4$ , right) in B3LYP 6-31G(d) transition structures for eight structurally distinct H-bond donor catalysts. This analysis points to differential iminium ion stabilization through hydrogen bonding interactions as a basis for enantioselectivity.

**Figure 11:** Representative asymmetric Povarov reaction catalyzed by urea **20**. Illustrated below are the hydrogen bonding interactions that lead to the strong binding observed between the **20** and the iminium sulfonate intermediate.

**Figure 12:** Plots of initial rate and enantiomeric excess in the Povarov reaction versus [**21**] at three different concentrations of triflic acid. This graph was reproduced from reference 54.

**Figure 13:** Calculated transition states structures for the Povarov reaction catalyzed by **21**. A stabilizing, transition state  $\pi$ - $\pi$  interaction is proposed as a basis for enantioselectivity, and is highlighted in the structure leading the (*R*) enantiomer of product.

## Table Titles

**Table 1:** Distance-dependencies of non-covalent interactions. The dependencies for entries 2–5 are only valid at values of  $r$  several times greater than the lengths of the interacting dipoles. At or near the Van der Waals distances operating in the catalytic reactions discussed in the text, these interactions become largely electrostatic, displaying a  $\sim 1/r$  dependence.

**Table 2:** Effect of catalyst arene substituents on the enantioselectivity of Claisen rearrangement of **1** is consistent with the proposed transition state cation- $\pi$  interaction.